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(54) **Use of 2-(3,4-dimethoxycinnamoyl)-aminobenzoic acid for the manufacture of a medicament for the treatment of restenosis.**

(57) This invention provides the use of Tranilast or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the treatment or prevention of restenosis associated with coronary intervention. A 600 mg dosage of Tranilast for a treatment period of three consecutive months after coronary intervention lowers the incidence of restenosis, and reduces the degree of stenosis in patients.

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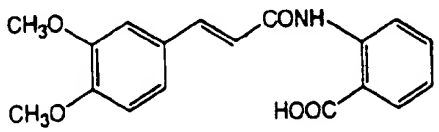
The present invention relates to the use of 2-(3,4-dimethoxycinnamoyl)aminobenzoic acid (Tranilast) as a therapeutic agent for the treatment or prevention of restenosis associated with coronary intervention.

More particularly, the present invention relates to the use of 2-(3,4-dimethoxycinnamoyl)aminobenzoic acid (Tranilast), or a pharmaceutically acceptable salt thereof, represented by the formula:



(I)

for the manufacture of a pharmaceutical composition for the treatment or prevention of restenosis associated with coronary intervention.

Illustrative of pharmaceutically acceptable salts are inorganic salts such as the sodium or calcium salt, or organic salts formed with amines such as morpholine, piperidine and arginine.

Coronary intervention includes for example, Percutaneous Transluminal Coronary Angioplasty (PTCA), Direction Coronary Atherectomy and Stent.

Coronary intervention is a surgical approach to the treatment of ischemic heart diseases such as angina pectoris and myocardial infarction. Coronary intervention technically involves mechanical revascularization of a stenosed lesion in a coronary artery by means of, for example, a balloon catheter or an atherectomy catheter. As a consequence, coronary intervention often causes restenosis due to damaged intima cells.

Up to the present time, there has not been any effective drug for the treatment or prevention of restenosis associated with coronary intervention.

Tranilast is sold commercially as a drug for the treatment of allergic diseases, e.g., allergic bronchitis, allergic asthma and atopic dermatitis, based on the activity exhibited by the drug for inhibiting the release of chemical mediators [The Journal of Allergy and Clinical Immunology, Vol. 57, No. 5, pp. 396-407, (1976)].

Recently, in Biochemical Pharmacology, Vol.36, No. 4, pp. 469-474 (1987), it was reported that Tranilast inhibits fibroblast proliferation and collagen accumulation.

Further, it is noted of record that the authors of the present invention embodiments reported in the Japanese College of Cardiology (1988) the treatment of patients subjected to PTCA surgery with Tranilast in a daily oral dose of 300 mg for 30 consecutive days after PTCA surgery. The clinical data did not indicate any significant efficacy in preventing a restenosis effect associated with PTCA surgery.

The present invention provides the use of 2-(3,4-dimethoxycinnamoyl)aminobenzoic acid, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the prevention or treatment of restenosis associated with coronary intervention.

Other features and advantages of the present invention will become apparent from the following description and examples.

It is documented that restenosis associated with coronary intervention occurs within a period of about six months after coronary intervention. The clinical test data described above were obtained over a test period of 30 consecutive days after the PTCA surgery. It was speculated by the present inventors that the lack of any significant efficacy in preventing a restenosis effect with Tranilast might be due to the relatively short 30 day duration of the drug treatment after PTCA surgery.

Further clinical testing of patients was conducted to determine if an extended period of Tranilast treatment might be effective for lowering the incidence of post-surgery restenosis associated with PTCA. It was found that Tranilast dosage of patients for a duration of at least about three months (i.e., a term of at least about 90 consecutive days of treatment) reduced the incidence of restenosis associated with the PTCA surgery.

In one clinical study, when patients were administered Tranilast in a daily oral dose of 600 mg for three consecutive months after PTCA surgery, the incidence of restenosis was less than about 20%.

The incidence of restenosis associated with PTCA surgery usually is about 40%, as reported in Percutaneous Transluminal Coronary Angioplasty, page 179 (1990). Thus, the present invention demonstrates that Tranilast dosage of patients after PTCA surgery is effective in reducing the incidence of restenosis during the treatment period. In patients in which the incidence of restenosis occurs when under Tranilast treatment, the mean degree of stenosis is minimized. The need for a second PTCA intervention is significantly reduced.

When Tranilast or a pharmaceutically acceptable salt thereof is employed therapeutically, it can be administered orally or parenterally in appropriate dosage forms, such as powder, granules, tablets, capsules and injectable solutions.

A Tranilast pharmaceutical composition can be formulated by admixing suitable carriers such as exci-

pients, disintegrators, binders and brighteners,

and preparing in accordance with conventional molding methods and dosage forms.

For example, a powder dosage form can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof with suitable excipients, binders and brighteners.

Tablets can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof with suitable excipients, disintegrators, binders and brighteners,

and compressing the mixture with conventional molding equipment. The tablets also can be coated to provide film-coated tablets, sugar-coated tablets and enteric coated tablets.

Capsules can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof with suitable excipients and brighteners, and filling the mixture into capsules, or by forming granules containing Tranilast or a pharmaceutically acceptable salt thereof with conventional molding equipment, and filling the formed granules into capsules.

When a pharmaceutical composition of the present invention is employed therapeutically, the dosage of Tranilast or a pharmaceutically acceptable salt thereof as an active ingredient can be in a range between about 300-1000 mg. A preferred dosage is between about 300-600 mg per adult patient by oral administration on a daily basis for a treatment period of about 3-6 consecutive months after coronary intervention. The dosage and a term of administration are changed depending, for example, upon the weight and age and sex of the patient and the severity of the condition to be treated.

The present invention is further illustrated in more detail by way of the following Examples.

EXAMPLE I

This Example demonstrates the efficacy of the invention in the treatment of restenosis associated with PTCA surgery.

One hundred and forty nine patients with lesions with a partial occlusion, underwent successful PTCA procedures with smooth dilation, and enrolled in this study. These patients were divided into two groups, and both groups did not differ significantly with sex, distribution of coronary arteries and ratio of lesions restenosed after PTCA; One group (49 lesions) received Tranilast in a daily dose of 600 mg (hereinafter identified as the R group), and the other group (100 lesions) did not receive Tranilast (hereinafter identified as the C group). In addition, all patients were also given calcium antagonists, nitrites and anti-platelets. These drugs were administered for 3 consecutive months after PTCA, and follow-up coronary angiography was performed 3 months after PTCA.

The measurements were made in two projections using a direct caliper system, and all measurements (before and immediately after PTCA and at final follow-up) were made in the same projection for more accurate comparison.

Diameter stenosis was calculated as the mean of the measurements, and restenosis was defined as a loss of at least 50% of the initial gain in luminal diameter accomplished by dilation.

A. The ratio of female-to-male, distribution of coronary vessels, and the ratio of lesions restenosed after PTCA were as follows.

(1) The ratio of female-to-male

R group : 18% ; C group : 29%

(2) Distribution of coronary vessel

(R group and C group)

left anterior descending artery :

left circumflex artery : right coronary artery = 1:1:1

(3) The ratio of lesions restenosed after PTCA

R group : 49.0% ; C group : 35.6%

B. The results of examination were as follows.

(1) The change of stenosis diameter

Pre-PTCA

R group : 68.4% ± 12.3% ;

C group : 71.1% ± 11.5%, ns

Post-PTCA

R group : 14.8% ± 11.6% ;

C group : 18.5% ± 11.0%, ns

Three months after PTCA

R group : 25.8% ± 18.2% ;

C group : 41.2% ± 26.8%, ($p < 0.001$)

(2) The incidence of restenosis

R group : 12.2% ; C group : 38.0% ($p < 0.01$)

The comparative clinical data demonstrate the efficacy of 3 month Tranilast treatment for the prevention of restenosis in patients after PTCA surgery. The following comparative Example demonstrates that a one month Tranilast treatment is not effective for reducing restenosis in patients after PTCA surgery.

EXAMPLE II

This Example illustrates a one month treatment of patients with Tranilast which is not effective for reducing the incidence of restenosis associated with PTCA surgery.

Three hundred and fifty two patients with lesions with a partial occlusion, underwent successful PTCA procedures with smooth dilation, and enrolled in this study. These patients were divided into two groups, and both groups did not differ significantly with sex, age, number of diseased vessels, distribution of coronary arteries and mean degree of stenosis (%) before PTCA ; One group (100 lesions) received Tranilast in a daily dose of 300 mg for 30 consecutive months (hereinafter identified as the R' group), and the other group (252 lesions) did not receive Tranilast (hereinafter identified as the C' group). In addition, all patients were also given calcium antagonists, vasodilators and anti-platelets for 3 consecutive months after PTCA. Follow-up coronary angiography was performed 3 months after PTCA.

The measurements were made in two projections using a direct caliper system, and all measurements (before and immediately after PTCA and at final follow-up) were made in the same projection for more accurate comparison.

Diameter stenosis was calculated as the mean of the measurements, and restenosis was defined as a loss of at least 50% of the initial gain in luminal diameter accomplished by dilation.

The results of examination were as follows.

(1) The chance of stenosis diameter

Pre-PTCA

R' group : 86.1% ; C' group : 78.7%, ns

Post-PTCA

R' group : 78.4% ; C' group : 22.5%, ns

Three months after PTCA

R' group : 78.4% ; C' group : 74.9%, ns

(2) The incidence of restenosis

R' group : 32.1% ; C' group : 36.1%, ns

The one month treatment with a 300 mg dosage did not have a significant effect in reducing the incidence of restenosis in patients after PTCA surgery.

Claims

1. The use of 2-(3,4-dimethoxycinnamoyl)aminobenzoic acid or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the treatment or prevention of restenosis associated with coronary intervention.

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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	CARDIOLOGIA vol. 36, no. 12, 1991, pages 309 - 320 ANTONIO MARZOCCHI ET AL. 'La ristenosi dopo angioplastica coronarica: patogenesi e profilassi' * abstract *	1	A61K31/165
D,Y	BIOCHEMICAL PHARMACOLOGY vol. 36, no. 4, 1987, pages 469 - 474 MASAYUKI ISAJI ET AL. 'Selective inhibition of collagen accumulation by N-(3,4-dimethoxycinnamoyl)anthranilic acid (N-5') in granulation tissue' * abstract *	1	
P,Y	J.VASC.RES. vol. 30, no. 2, 1993, pages 108 - 115 PAUL D. BONIN ET AL. 'Inhibition of fibroblast and smooth muscle cell proliferation and migration in vitro by a novel aminochromone U-67154' * abstract *	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K
A	TRENDS CARDIOVAS. MED. vol. 2, no. 3, 1992, pages 90 - 94 JAMES A. FAGIN ET AL. 'Growth factors, cytokines and vascular injury' * page 91 * * abstract *	1	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	04 JANUARY 1994	TZSCHOPPE D. A.

CATEGORY OF CITED DOCUMENTS

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D : document cited in the application
L : document cited for other reasons

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	AURIS,NASUS,LARYNX vol. 19, no. 1, 1992, pages 55 - 61 NAOBUMI NONOMURA ET AL. 'A case of pharyngolaryngeal stenosis in Behcet's disease' ----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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MUNICH	04 JANUARY 1994	TZSCHOPPE D. A.

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X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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